Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels

The document entitled "Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels" has been prepared and submitted for review to the Deputy Director for Scientific Affairs. The document presents inhalation reference exposure levels (RELs) for 120 substances (Table 1). For those substances of multi-pathway exposure concern, oral reference exposure levels are also included.

There are several notable features of the chronic REL document.

■ Formalized peer review program

This document has undergone internal peer review by OEHHA, ARB, and CAPCOA staff. Comments from USEPA were also received on the document and incorporated. This document will be reviewed by an advisory committee of non-governmental scientists (Scientific Review Panel).

■ Input from risk managers and from external stakeholders

This document has been reviewed by risk managers of the Cal/EPA Boards and Departments, and by representatives of Air Quality Management and Air Pollution Control Districts as part of the California Air Pollution Control Officers Association review. The document will be distributed for comment to others, including external stakeholders.

■ Coordination of effort with U.S. EPA.

The project made use of all available risk assessment information from U.S. EPA and other authoritative bodies. All 43 relevant U.S. EPA reference concentrations (RfCs) were adopted as RELs. U.S. EPA RfC and U.S. EPA reference dose (RfD) methods were followed in the development of 76 new proposed RELs. Two values previously adopted by the ARB after SRP review are also summarized in the document.

■ Balance level of effort with importance

The selection of chemicals for intensive review in this document was based in part on the importance of the chemical within California. Emphasis was placed on developing health levels for those substances with high emissions or of concern to risk managers. The project incorporated all available risk assessment information from U.S. EPA

■ Uncertainty factors: Incorporate consideration of effect severity

Concerns that severely adverse and high incidence effects should be accounted for differently than mild and/or rarely encountered effects were addressed by incorporation of

an intermediate (3-fold rather than 10-fold) LOAEL to NOAEL uncertainty factor for 17 compounds. Similarly, concerns that 10-fold subchronic to chronic uncertainty factors were not appropriate for longer-term subchronic data were addressed, and a 3-fold subchronic uncertainty factor was used for 23 substances.

■ A comparison of U.S. EPA RfCs and additional RELs estimated by OEHHA as presented in this document indicates that the OEHHA RELs are similar to values developed by U.S. EPA (Table 2). Cumulative uncertainty factors for OEHHA RELs were smaller than those for U.S. EPA RfCs. The primary difference appears to be the more frequent use by USEPA of an additional 3 to 10-fold database deficiency factor.

■ The OEHHA REL development process emphasized the use of human exposure data whenever possible (Table 3). This result was achieved even though the additional chemicals evaluated by OEHHA might be anticipated to have less comprehensive health data than those previously selected by U.S. EPA for RfC development.

Table 1. Proposed OEHHA Chronic Inhalation REL Summary

Substance	*Listed in CAPCOA (1993)*	*U.S. EPA RfC*	*Chronic Inhalation REL ($\mu g/m^3$)*	*Hazard Index Target Organ(s)*	*Human Data*
Acetaldehyde*	☑	☑	9	Respiratory system	
Acrolein	☑	☑	0.02	Respiratory system; eyes	
Acrylamide	☑		0.7	Nervous system	
Acrylic acid		☑	1	Respiratory system	
Acrylonitrile	☑	☑	2	Respiratory system	
Allyl chloride		☑	1	Nervous system	
Ammonia	☑	☑	100	Respiratory system	☑
Aniline		☑	1	Cardiovascular system	
Antimony trioxide		☑	0.2	Respiratory system	
Arsenic & arsenic compounds	☑		0.03	Development; cardiovascular system; nervous system	
Arsine		☑	0.05	Cardiovascular system	
Benzene	☑		60	Cardiovascular system; development; nervous system; immune system	☑
Benzidine	☑		10	Nervous system; alimentary system	
Beryllium & beryllium compounds	☑		0.001	Respiratory system	☑
Butadiene (1,3-)			8	Reproductive system	
Cadmium & cadmium compounds	☑		0.01	Kidney; respiratory system	☑
Carbon disulfide		☑	700	Nervous system; reproductive system	☑
Carbon tetrachloride	☑		40	Alimentary system; development; nervous system	
Chlorinated dioxins & dibenzofurans	☑		0.00004	Alimentary system; immune system; reproductive system; development; endocrine system; respiratory system; cardiovascular system	
Chlorine	☑		0.06	Respiratory system	
Chlorine dioxide		☑	0.2	Respiratory system	
Chloroacetophenone (2-)		☑	0.03	Respiratory system	

Table 1. Proposed OEHHA Chronic Inhalation REL Summary (continued)

Substance	*Listed in CAPCOA (1993)*	*U.S. EPA RfC*	*Chronic Inhalation REL ($\mu g/m^3$)*	*Hazard Index Target Organ(s)*	*Human Data*
Chlorobenzene	☑		1,000	Alimentary system; kidney; reproductive system	
Chlorodifluoromethane	☑	☑	50,000	Development; kidney; endocrine system	
Chloroform	☑		300	Alimentary system; kidney; development	
Chloropicrin	☑		4	Respiratory system	
Chromium (VI)	☑		0.0008	Respiratory system	☑
Cobalt & cobalt compounds			0.005	Respiratory system	
Copper & copper compounds	☑		0.02	Respiratory system	☑
Cresol mixtures	☑		4	Cardiovascular system	
Dichlorobenzene (1,4-)	☑	☑	800	Nervous system; respiratory system; alimentary system; kidney	
Dichlorodifluoro-methane	☑		1,000	Alimentary system	
Dichloroethylene (1,1-)	☑		20	Alimentary system	
Diethanolamine			20	Cardiovascular system; nervous system	
Di(2-ethylhexyl)-phthalate	☑		10	Alimentary system; respiratory system	
Dimethylformamide (N,N-)		☑	30	Alimentary system	☑
Dinitrotoluene (2,4-)			7	Nervous system; alimentary system	
Dioxane (1,4-)	☑		3,000	Alimentary system; kidney; cardiovascular system	
Epichlorohydrin	☑	☑	1	Respiratory system; eyes	
Epoxybutane (1,2-)		☑	20	Respiratory system; cardiovascular system	
Ethylbenzene		☑	1,000	Development; alimentary system; kidney	
Ethyl chloride	☑	☑	10,000	Development; alimentary system	

Table 1. *Proposed OEHHA Chronic Inhalation REL Summary (continued)*

Substance	*Listed in CAPCOA (1993)*	*U.S. EPA RfC*	*Chronic Inhalation REL ($\mu g/m^3$)*	*Hazard Index Target Organ(s)*	*Human Data*
Ethylene			100	Cardiovascular system; immune system	☑
Ethylene dibromide	☑		0.8	Reproductive system	☑
Ethylene dichloride	☑		400	Alimentary system; nervous system	
Ethylene glycol			400	Respiratory system; eyes; kidney; development	☑
Ethylene glycol butyl ether	☑		200	Cardiovascular system	
Ethylene glycol ethyl ether	☑	☑	200	Reproductive system; cardiovascular system	
Ethylene glycol ethyl ether acetate	☑		300	Development	
Ethylene glycol methyl ether	☑	☑	20	Reproductive system	
Ethylene glycol methyl ether acetate	☑		90	Reproductive system	
Ethylene oxide	☑		5	Cardiovascular system; respiratory system; nervous system	☑
Ethylenethiourea			3	Endocrine system; alimentary system	
Fluorides & hydrogen fluoride	☑		30	Bone; respiratory system	☑
Formaldehyde	☑		2	Respiratory system; eyes	☑
Glutaraldehyde	☑		0.1	Respiratory system	
Hexachlorobenzene	☑		3	Alimentary system	
Hexachlorobutadiene			90	Alimentary system; kidney	
Hexachlorocyclohexane (α-)			20	Alimentary system	
Hexachlorocyclohexane (β-)			2	Immune system; reproductive system	
Hexachlorocyclohexane (γ-)	☑		0.3	Kidney	
Hexachlorocyclopentadiene	☑		0.7	Respiratory system	

Table 1. Proposed OEHHA Chronic Inhalation REL Summary (continued)

Substance	*Listed in CAPCOA (1993)*	*U.S. EPA RfC*	*Chronic Inhalation REL ($\mu g/m^3$)*	*Hazard Index Target Organ(s)*	*Human Data*
Hexachloroethane			80	Nervous system; alimentary system; kidney	
Hexamethylenediiso-cyanate (1,6-)		☑	0.01	Respiratory system	
Hexane (n-)		☑	200	Nervous system	☑
Hydrazine	☑		0.2	Alimentary system; endocrine system	
Hydrogen chloride	☑	☑	7	Respiratory system	
Hydrogen cyanide	☑	☑	3	Cardiovascular system	☑
Hydrogen sulfide	☑	☑	0.9	Respiratory system	
Isophorone			2,000	Development; kidney; alimentary system	
Isopropanol			2,000	Nervous system; blood; alimentary system	
Maleic anhydride	☑		0.2	Respiratory system	
Manganese & manganese compounds	☑	☑	0.05	Nervous system	☑
Mercury & mercury compounds	☑	☑	0.3	Nervous system	☑
Methanol	☑		10,000	Development	
Methyl bromide	☑	☑	5	Respiratory system; nervous system; development	
Methyl t-butyl ether		☑	3,000	Kidney; eyes; alimentary system	
Methyl chloroform	☑		1,000	Nervous system	
Methylene chloride	☑		300	Cardiovascular system; nervous system	☑
Methylene dianiline	☑		20	Eyes; alimentary system	
Methylene diphenyl isocyanate (polymeric)		☑	0.02	Respiratory system	
Methyl ethyl ketone		☑	1000	Reproductive system	
Methyl isocyanate	☑		1	Respiratory system; reproductive system	
Methyl methacrylate	☑		100	Respiratory system; nervous system	
Naphthalene	☑		9	Respiratory system	

Table 1. Proposed OEHHA Chronic Inhalation REL Summary (continued)

Substance	*Listed in CAPCOA (1993)*	*U.S. EPA RfC*	*Chronic Inhalation REL ($\mu g/m^3$)*	*Hazard Index Target Organ(s)*	*Human Data*
Nickel & nickel compounds	☑		0.05	Respiratory system; immune system	
Nitric acid			40	Respiratory system	
Nitrobenzene	☑		30	Respiratory system	
Nitrogen dioxide	☑		20	Respiratory system	☑
Nitropropane (2-)	☑	☑	20	Alimentary system	
Pentachlorophenol	☑		100	Alimentary system; kidney; development	
Perchloroethylene*	☑		40	Alimentary system	
Phenol	☑		600	Alimentary system; cardiovascular system; kidney; nervous system	
Phosgene			0.3	Respiratory system	
Phosphine	☑	☑	0.3	Respiratory system; alimentary system; nervous system	
Phosphoric acid		☑	10	Respiratory system	
Phosphorus	☑		0.07	Reproductive system	
Phthalic anhydride	☑		10	Respiratory system	☑
Propylene			3,000	Respiratory system	
Propylene glycol monomethyl ether		☑	2,000	Nervous system	
Propylene oxide	☑	☑	3000	Respiratory system	
Selenium & selenium compounds	☑		0.08	Respiratory system	
Silver and compounds			20	Skin	☑
Sodium hydroxide	☑		2	Respiratory system; eyes	☑
Styrene	☑	☑	1,000	Nervous system	☑
Styrene oxide			6	Respiratory system	
Sulfuric acid			1	Respiratory system	
Tetrachlorophenol	☑		90	Alimentary system	
Toluene	☑	☑	400	Nervous system; alimentary system; development	☑
Toluene diisocyanates (2,4- & 2,6-)	☑	☑	0.07	Respiratory system	☑

Table 1. Proposed OEHHA Chronic Inhalation REL Summary (continued)

Substance	*Listed in CAPCOA (1993)*	*U.S. EPA RfC*	*Chronic Inhalation REL ($\mu g/m^3$)*	*Hazard Index Target Organ(s)*	*Human Data*
Trichloroethane (1,1,2-)			400	Alimentary system; kidney; nervous system; cardiovascular system	
Trichloroethylene	☑		600	Nervous system; eyes	☑
Trichlorofluoromethane	☑		20,000	Nervous system	
Trichloro-1,2,2-trifluoroethane (1,1,2-)	☑		90,000	Nervous system	
Triethylamine		☑	7	Respiratory system; immune system; eyes	
Vinyl acetate		☑	200	Respiratory system	
Vinyl bromide		☑	7	Alimentary system	
Vinyl chloride	☑		5	Alimentary system; nervous system	☑
Xylenes (m-, o-, p-)	☑		200	Nervous system; respiratory system	☑
Zinc & zinc compounds	☑		0.9	Respiratory system; immune system	☑

*Reference exposure levels previously reviewed by the Scientific Review Panel and adopted by the Air Resources Board under the Toxic Air Contaminant program.

Table 2. Geometric Mean of the Uncertainty Factors Incorporated for Proposed OEHHA Chronic Inhalation RELs and U.S. EPA RfCs

Uncertainty Factor	***OEHHA RELs Derived from Inhalation Data***	***U.S. EPA RfCs***
LOAEL	2.6	1.9
Subchronic	2.2	2.1
Interspecies	2.4	2.7
Intraspecies	9.3	8.9
Modifying factor	1.0	2.4
Cumulative	134	238

Table 3. Comparison of Relative Use of Human and Animal Data in Deriving U.S. EPA RELs and Proposed OEHHA Chronic Inhalation RELs

Reference Level	***Human data***	***Animal data***
U.S. EPA RfCs	9/43 (21%)	33/43 (79%)
Proposed OEHHA chronic inhalation RELs (derived from inhalation data)	19/63 (30%)	43/63 (70%)
Proposed OEHHA chronic inhalation REL (including those derived from non-inhalation data)	20/75 (27%)	56/75 (73%)
Overall	29/118 (25%)	89/118 (75%)